New ultrasonographic screening method for oropharyngeal dysphagia

Tissue Doppler imaging

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ABSTRACT

Background: Ultrasound Tissue Doppler imaging (US-TDI) has been used to diagnose regional wall motion (WM) abnormalities in coronary artery disease, but has not been applied to oropharyngeal diseases. This study aimed first to validate an US-TDI method to assess cervical esophageal (CE) WM, and secondly to use the method to evaluate CE WM in patients with oropharyngeal dysphagia (OD).

Methods: First, we enrolled 22 healthy men (mean age: 59.7 years) who all underwent both US-TDI and videofluoroscopy (VF) and then esophageal high-resolution manometry (HRM) in the same week. We evaluated the reproducibility of the US-TDI, and the relationship between US-TDI and other modalities (VF and HRM). Second, we enrolled 56 mild OD patients (mean age: 58.0 years) and age- and sex-matched healthy controls.

Results: All healthy subjects underwent US-TDI, VF, and HRM successfully, with a sufficiently high reproducibility coefficient for this method, and significant correlation between US-TDI and VF/HRM parameters. US-TDI showed mean time to open CE wall and mean velocity of CE wall opening significantly differed between patients and healthy controls ($P<0.01$).

Conclusion: We have developed a US-TDI method for easily assessing CE WM in daily practice, and also found significant differences in CE WM between mild OD patients and healthy controls.

Keywords: cervical esophagus; high-resolution manometry; oropharyngeal dysphagia; Ultrason Tissue Doppler imaging; videofluoroscopy
New & Noteworthy: New ultrasonographic screening method using tissue Doppler imaging for oropharyngeal dysphagia was found to be reliable, reproducible and well-tolerated method. There is a significant correlation between this new method and conventional methods. This method revealed that patients having mild symptom of oropharyngeal dysphagia had already significantly delayed cervical esophageal wall opening.

INTRODUCTION

Oropharyngeal dysphagia (OD)—swallowing difficulty—is a growing health concern in globally aging population. Age-related changes in swallowing physiology as well as age-related diseases are predisposing factors for dysphagia in elderly people. In the United States, OD affects 300,000 to 600,000 persons annually (20). Although the exact prevalence of dysphagia across different settings is unclear, conservative estimates suggest that 15% of the elderly population is affected by OD (1). OD is a common condition and is associated with aspiration, dehydration, nutritional and respiratory complications and even death. However, most patients are not diagnosed and do not receive any treatment.

OD begins with minor symptoms, such as laryngopharyngeal dysesthesia or unusual sensations during swallowing. Furthermore, even mild symptom of OD would lead to decrease patients’ quality of life (QOL) (14,21), and therefore warrants caution. OD may present few specific clinical signs and must be confirmed by videofluoroscopy (VF), esophageal manometry or endoscopy (21). However, existing modalities to assess oropharyngeal motility have such drawbacks as high costs, radiation exposure, or intricacy. Doppler echocardiography relies on detecting changes in ultrasound signal frequency reflected from moving objects, using conventional Doppler principles to assess the velocity
of blood flow by measuring high-frequency, low-amplitude signals from small, fast-moving blood cells (14). With recent technological advances, tissue Doppler imaging (TDI) has emerged as an adjunct tool in diagnosing regional wall motion (WM) abnormalities in coronary artery disease (13,24). In TDI, the same Doppler principles are used to quantify higher-amplitude, lower-velocity signals of myocardial tissue motion (Figure 1). However, TDI has not been applied to functional diseases of the cervical esophagus (CE). To assess CE WM easily and objectively, we have developed, for the first time, an ultrasonographic method using TDI (US-TDI).

The aims of this study were first to validate a US-TDI method, and secondly to use this method to evaluate CE WM in OD patients. This study was approved by the local ethics committee (No. 1171) and registered as UMIN000014403.

SUBJECTS AND METHODS

Subjects

First, we enrolled 22 healthy men (mean age: 59.7 years). Inclusion criteria were: aged over 20 years; no known disease that affected swallowing; and written informed consent to participate. Exclusion criteria were: presence of disease that affected swallowing; history of surgery or radiotherapy involving the upper airways; neurological diseases such as Parkinson’s disease or multiple sclerosis; psychiatric disorder; gastrointestinal disease such as gastroesophageal reflux disease and hiatal hernia; or otorhinolaryngological disease (such as Zenker’s diverticulum and laryngeal palsy) that affect swallowing. No subjects needed to be excluded. Informed consent was obtained from all subjects. The experiment
adhered to the tenets of the Declaration of Helsinki, and was approved by our institutional ethics committee.

We then enrolled 56 consecutive patients who complained of OD (26 men and 30 women; mean age: 58.0 ± 13.7 years). All of the patients answered our previously validated questionnaire about gastrointestinal symptoms (8,18) and their scores of symptoms regarding OD were 4 points or more (0=none, 1=extremely rare, 3=rare, 4=sometimes, 5=often, 6=always) on a seven-grade Likert scale. Enrolled patients met the following inclusion criteria: [1] older than 20 years of age; and [2] provision of written informed consent for study participation. Exclusion criteria were: [1] history of surgery or radiotherapy involving the upper airways; [2] presence of psychiatric disorder; [3] having received a prokinetic agent within 1 month before enrollment; [4] use of an antipsychotic drug or skeletal muscle relaxant. Underlying diseases/conditions were identified through a review of the medical records. Of all patients, 14 had a neurological history (10 patients with minor stroke, 3 with Parkinson’s disease, and 1 with Alzheimer’s disease), and 42 patients had unknown etiologies at the time of the study. We also recruited 56 healthy volunteers (26 men and 30 women; mean age: 59.7 ± 16.7 years) from our campus, who were paid to undergo testing as normal controls. The volunteers underwent medical history and physical examinations, and were only enrolled if they had no organic diseases or globus sensation.

**Methods**

First, all 22 healthy subjects initially underwent US-TDI in the morning. Then, VF was performed one hour after US-TDI procedure. Finally, high-resolution esophageal
manometry (HRM) was also performed for all subjects within one week. Two physicians (NM and JH) performed the US-TDI; neither physician informed the other of test results in advance. We then evaluated the reproducibility of the US-TDI, and the relationship between US-TDI and VF/HRM.

Second, US-TDI was performed for both OD patients and healthy volunteers. Each subject was studied in the morning. Their CE WM was evaluated by US-TDI and compared with age- and sex-matched healthy volunteers.

1) **US-TDI**

Without any preparation, each test was conducted with the subject in the sitting-upright position and at least 30 minutes after taking a meal, to prevent vomiting. The apparatus used was Aplio XG (Toshiba Medical Systems Co., LTD. Tochigi, Japan) with 12.0 MHz linear array transducer. Each subject underwent this procedure in the morning. With the subject in a sitting position, the transducer was placed on the left side of the neck to obtain an axial view of the CE, located 1 cm below the lower border of the cricoid cartilage.

During observation of CE WM by the US-TDI, subjects were instructed to swallow 5cc of a viscous room-temperature test food delivered with a syringe five times, with 1-minute intervals between delivery. The test food used was Weider in Jelly® (Morinaga & Co., Ltd. Tokyo, Japan), which is commercially available in Japan. The US-TDI data were stored as raw data and analyzed using the TDI-Q software (Toshiba Medical Systems Co., LTD. Tochigi, Japan) incorporated in the equipment. At the TDI-Q analyses of CE WM, both time–displacement and time–velocity curves of CE wall movement were automatically calculated and depicted.
Figure 2 shows representative TDI-Q-generated (a) time–displacement and (b) time–velocity curves of CE WM of one subject. The time-velocity curve shows two peaks of positive and negative waveforms during one swallow. The positive waveform corresponds to the velocity of CE wall opening, and the negative wave corresponds to the velocity of CE wall closing. In this study, CE WM was evaluated with five parameters in Figure 2: maximum moving distance of the anterior CE wall, duration and velocity of CE wall opening, and duration and velocity of CE wall closing.

Parameters used in this experiment included [1] maximal move distance (mm); [2] CE wall opening time (msec); [3] CE wall closing time (msec); [4] velocity to open CE wall (mm/sec); and [5] velocity to close CE wall (mm/sec).

Reproducibility of the US-TDI was first evaluated with different examiners on the same day with the same subjects (n=10); then with the same examiner on the same day with different subjects (n = 10); and finally with the same examiner and same subjects on different days (n = 10).

2) VF

All subjects sat in a chair with a backrest for 80-degree hip joint flexure and a pillow headrest to maintain the craniocervical position. The lateral VF images were captured and recorded on a DVD. Images were obtained for each subject performing free swallowing of 5 mL of barium-containing material from a cup in two iterations. The timing of first superior movement of the hyoid bone was used to mark the timing of swallow onset. The position of the proximal upper esophageal sphincter (UES) was identified by visualization of the tracheal air column. Then, timing of opening and closing of UES were measured,
glossopalatal junction opening being given the time value 0 according to the previous
study by Rofes L, et al (15). Image analysis was performed with Image J processing
software developed at the US NIH (Bethesda, MD).

3) HRM

HRM was performed with a Sandhill Scientific INSIGHT G3 using UNI HRiM Probe
(Sandhill Scientific, Highlands Ranch, CO, USA). All patients refrained from midday
meals, and examinations were performed in the afternoon. HRM was performed with the
patient in the seated position as described previously (19). A total of 32 solid-state pressure
sensors, including 14 circumferential (located at 5, 15, 20, 25, and 30 cm from the tip) and
18 directional pressure sensors (at 10 and 35 cm), were used. The UNI HRiM Probe was
inserted transnasally into the esophagus to a depth of 60 cm. First, the lower esophageal
sphincter was identified to calibrate the HRM topography imagery. A command swallow of
a 5-mL bolus of room-temperature viscous food was performed 10 times, and internal
pressure was measured. The test food used was Weider in Jelly® (Moringa & Co., Ltd.
Tokyo, Japan), which is the same as that used in US-TDI study.

The UES relaxation time was calculated according to the method described by Kahrilas et
al (7): the beginning and end of the relaxation is determined by searching in two directions
from the nadir until a pressure equal to 50% of the predetermined resting UES pressure is
located. Therefore, the duration of relaxation is defined as the time during which the
sphincter is at least 50% relaxed. Pharyngeal pressure was defined as the maximal
amplitude pressure from pharynx to larynx. Velopharyngeal and meso-hypopharyngeal
muscle zone were identified according to the method by Takahashi, et al (17). Swallowing
Pressure was defined as the highest pressure in the meso-hypopharyngeal muscle zone. We evaluated UES relaxation time and swallowing pressure.

**Statistical analysis**

Data are expressed as the mean ± standard deviation (SD). Spearman correlation analysis was used to assess the intra- and inter-observer reproducibility of the US-TDI method. The Bland–Altman limits of agreement (2) were used to assess the inter-modality correlation (US-TDI and VF). Spearman correlation analysis was also used to assess the inter-modality correlation (US-TDI and HRM). Correlation coefficients were classified as follows: 0.00 to 0.19, very weak; 0.20 to 0.39, weak; 0.40 to 0.59, moderate; 0.60 to 0.79, strong; and 0.80 to 1.00, very strong. The Mann–Whitney U test was used to compare two independent groups. \( P < 0.05 \) was considered significant. Statistical processing was conducted using the software SPSS statistical package release 17.0 (SPSS Inc., Chicago, IL, USA).

**RESULTS**

All subjects underwent US-TDI, VF and HRM successfully and provided satisfactory data. The reproducibility coefficients of time to open CE wall by US-TDI were 0.88 (95% confidence interval [CI]: 0.85–0.92, \( P < 0.01 \); different examiner, same subjects, same day, \( n=10 \)), 0.89 (95% CI: 0.62–0.98, \( P < 0.01 \); same examiner, different subjects, same days, \( n=10 \)) and 0.80 (95% CI: 0.68–0.98, \( P < 0.01 \); same examiner, same subjects, different days, \( n=10 \)). The reproducibility coefficients of the maximal move distance by US-TDI were 0.81 (95% CI: 0.37–0.95, \( P < 0.01 \); different examiner, same subjects, same day, \( n=10 \)), 0.75 (95% CI: 0.23–0.94, \( P < 0.01 \); same examiner, different subjects, same days,
n=10), and 0.80 (95% CI: 0.68–0.98, \( P < 0.01 \); same examiner, same subjects, different days, \( n=10 \)). The reproducibility coefficients of the CE wall closing time by US-TDI were 0.86 (95% CI: 0.44–0.97, \( P < 0.01 \); different examiner, same subjects, same day, \( n=10 \)), 0.89 (95% CI: 0.62–0.98, \( P < 0.01 \); same examiner, different subjects, same days, \( n=10 \)), and 0.61 (95% CI: 0.03–0.90, \( P = 0.05 \); same examiner, same subjects, different days, \( n=10 \)). Based on the above study results, we concluded that this method has high reproducibility.

There is a significant positive correlation between duration of CE wall opening by US-TDI and duration of UES opening by VF (\( r=0.86, P<0.001 \)) (Figure 3(a)). The mean difference was \( -14.6 \) msec (95% CI: \( -26.4 \)–\( -2.8 \)), which fits within the Bland–Altman limit of agreements (\( -68.0 \)–\( 38.8 \)) (Figure 3(b)). Figure 4(a) and (b) show a significant positive correlation between duration of CE wall opening by US-TDI and duration of UES opening by HRM (\( r=0.78, P<0.001 \)). The mean difference was \( -7.68 \) msec (95% CI: \( -47.5 \)–\( 32.1 \)), which also fits within the Bland–Altman limit of agreements (\( -183.1 \)–\( 167.7 \)). Figure 5(a) and (b) show the Bland–Altman plots for US-TDI versus VF/HRM for the UES closing time, respectively, showing that these mean differences also fit within the Bland–Altman limits of agreement. Figure 6 shows a significant negative correlation between the time of CE wall opening by US-TDI and swallowing pressure by HRM (\( r=-0.62, P=0.015 \)). These data confirm that the newly developed US-TDI method could be used to evaluate CE WM in place of the VF or HRM for clinical purposes.
Table 1 shows the differences in CE WM between OD patients and healthy volunteers. Mean symptom score of OD was 4.29 ± 0.46 in the OD patients group, while 0.48 ± 0.66 point in control group. Mean velocity to open the CE wall was significantly lower in the patient group than in the control group. Mean time to open the CE wall was significantly longer in the patient group than in the control group, although the other US-TDI parameters did not differ significantly between the two groups.

**DISCUSSION**

This study presents a newly developed non-invasive method of evaluating CE WM during swallowing using US-TDI. This method was also found to be reliable, reproducible and well-tolerated method that allows dynamic acquisition of functional measurements as the bolus across the CE.

This study also showed, using this US-TDI method, that patients having mild symptom of OD had already significantly delayed CE wall opening compared with healthy controls.

Although a few studies have evaluated swallowing function using ultrasonography (3,4,12), they mostly used the lingual movement (12) or the moving distance of bone (4) for indirect evaluation of swallowing function. However, these studies did not provide direct observation of swallowing movement. In contrast, the present study allows real-time observation of the bolus passing through the opened UES by external ultrasonographic observation of the CE, achieving indirect evaluation of swallowing movement.
Because ultrasonography is not limited by radiation exposure or examination site, and allows noninvasive testing, it is extremely useful in clinical practice. However, the quantitative evaluation in ultrasonography is difficult. In a previous ultrasonographic study, quantification was attempted by immobilizing the head (12). In this study, we used TDI for evaluation. Quantitative analysis of myocardial motion by TDI has been validated to be useful in evaluating myocardial function (11,23). TDI enables simple, quantitative and detailed evaluation of muscular movement. Our study demonstrated, for the first time, that evaluation of CE motility by TDI reflects swallowing function; and further, showed a significant difference in velocity of CE wall opening time between mild OD patients and healthy controls.

Recently, Morinière, et al. performed an ultrasound study to evaluate UES movement during swallowing in healthy subjects (9). They also assessed swallowing disorders involving the UES (Zenker's diverticulum, fibrosis, stricture) using this ultrasound method. Although we did not perform morphological measurements, we believe that this method could make both functional and morphological measurements. In fact, we identified one patient with Zenker's diverticulum in the CE while observing CE WM. The Morinière study had several differences in results to ours regarding the UES function. This might have been owing to differences in mean age of subjects, ultrasonographic parameters set in each study, and range and quantity of test meal, although we cannot say which causes are most important.
Subjects recruited in this second study had mild symptoms of OD. However, some showed delayed CE wall opening time. We speculated that some elderly people might have latent CE wall motility abnormalities even if they had mild symptoms of OD.

As displacement of UES is considered to be anterosuperior, observing UES movement in the same plane is difficult. However, in this study we focused on an axial view of the CE, located 1 cm below the lower border of the cricoid cartilage. Therefore, observing CE wall movement in the same plane is possible, because its movement is considered to be anterior.

Although we found that this US-TDI has high reproducibility, we did not elucidate factors that affect reproducibility of this method. An important factor is the experience of the US examiner; in this study, each of the two examiners had more than 20 years’ experience using US. Other important factors are apparatus, such as best probe selection and most appropriate setting. A learning curve was evident on applying this new technique. Trial and error was necessary to determine the best probe and the most appropriate setting. Aplio XG with an 8.0 MHz linear array transducer is to be optimal.

We used an energy gel (such as athletes use) as a test food in this study. We tried to choose a test food from an ordinary diet, because we would like to investigate CE WM in a real-life setting. The European Society for Swallowing Disorders concluded that evidence supports that increasing viscosity of food reduces risk of airway invasion and is a valid management strategy for OD (10), although new thickening agents should be developed to avoid the negative effects of increasing viscosity on residue, palatability, and treatment compliance. Therefore, energy gel was chosen for the food bolus to ensure good compliance, palatability, and avoidance of the other negative effects of increased viscosity.
as much as possible. We made five recordings for each subject, as swallowing exhibits inter and intra-individual variability. We believe that this method is applicable for patients with OD.

In this study, mean CE wall opening time was significantly lower in the patient group than in the control group, although their other US-TDI parameters did not significantly differ. We speculated that the swallowing pressure represents propulsive power for food gel going out from the oropharyngeal region to the CE (22). Patients with low swallowing pressure had weak propulsive power for gel going out from the oropharyngeal region to the CE, which led to multiple swallowing—i.e., longer time for the CE wall velocity to maximally open. OD begins with minor symptoms, such as a strange sensation during swallowing mimicking globus sensation (5,6). One recent study showed that abnormalities in only the esophageal phase were detected in patients with dysphagia without pre-established etiological damage (16). In this study, the patients with mild symptom of OD; possibly OD would begin with dysfunction of the CE wall opening, although further studies will be necessary to confirm this. Each parameter of US-TDI in patients with OD was evaluated according to sex and age. Male patients aged >65 years had a longer time to CE wall opening than male patients aged ≤65 years (638.7 ± 28.7 vs. 554.7 ± 18.7 msec, respectively; $P<0.05$). Conversely, there were no significant age-related differences in any parameter in female patients with OD. Accordingly, male patients with OD aged >65 years had the greatest US-TDI abnormality, although further large studies will be necessary to clarify this point.
The interval between undergoing US-TDI and then HRM for our subjects was 1 week in this study, because of our institutional condition. Previously, our study showed no significant differences in esophageal motility evaluated by HRM on a different day if the interval was within a week. In this regard, time intervals between US-TDI and HRM should not cause biases in this study.

The reproducibility and normal values for US-TDI among female patients remain unknown in this study. Further studies are required to confirm these parameters.

In conclusion, we have established, for the first time, a new method for assessing CE WM easily in daily practice, and have also found that the mean CE WM opening velocity is significantly lower in patients having mild symptom of OD than in healthy controls.

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REFERENCES


Figure 1. Explanation of TDI. In TDI, Doppler principles are used to quantify higher-amplitude, lower-velocity signals of tissue motion. Doppler echocardiography relies on detecting changes in ultrasound signal frequency as reflected from moving objects. In the present study, conventional Doppler principles were used to assess the velocity of blood flow by measuring high-frequency, low-amplitude signals from small, fast-moving blood cells using the moving target indication (MTI) filter as shown in (a). TDI has emerged as an adjunct tool in diagnosing regional wall motion abnormalities in coronary artery disease. In TDI, the same Doppler principles are used to quantify higher-amplitude, lower-velocity signals of myocardial tissue motion by using the MTI filter that cuts off the signals of small, fast-moving blood cells as shown in (b).

Figure 2. TDI-Q analysis of cervical esophageal wall movement showing (a) representative time–displacement curve and (b) representative time–velocity curve. CE: cervical esophagus; Tra: trachea; Thy: thyroid; Lt. CCA: left common carotid artery.

Figure 3. (a) Comparison of cervical esophageal wall opening time evaluated by US-TDI with upper esophageal sphincter opening time evaluated by VF, showing a significant positive correlation ($r=0.86, P<0.001$). (b) Comparison of these two parameters by the Bland–Altman method shows that the mean difference was small enough compared with the limit of agreements.

Figure 4. (a) Comparison of cervical esophageal wall opening time evaluated by US-TDI with upper esophageal sphincter opening time evaluated by HRM, showing significant positive correlation ($r=0.78, P<0.001$). (b) Comparison of these two parameters by the
Bland–Altman method shows the mean difference was small enough compared with the limit of agreements.

Figure 5. (a) Bland–Altman plots for US-TDI versus VF for UES closing time showing that this mean difference also fits within the Bland–Altman limit of agreements. (b) Bland–Altman plots for US-TDI versus HRM for UES closing time showing that this mean difference also fits within the Bland–Altman limit of agreements.

Figure 6. Comparison between cervical esophageal wall opening by US-TDI and swallowing pressure by HRM, showing a significant negative correlation.
Table 1. Comparison of cervical esophageal wall motion between patients with oropharyngeal dysphagia and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=56)</th>
<th>Controls (n=56)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal move distance (mm)</td>
<td>3.7 ± 1.9</td>
<td>3.6 ± 1.2</td>
<td>N.S.</td>
</tr>
<tr>
<td>Time to open cervical esophageal wall (msec)</td>
<td>626 ± 266</td>
<td>561 ± 105</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Time to close cervical esophageal wall (msec)</td>
<td>564 ± 126</td>
<td>572 ± 272</td>
<td>N.S.</td>
</tr>
<tr>
<td>Velocity of cervical esophageal wall to open (mm/sec)</td>
<td>12.2 ± 4.1</td>
<td>15.9 ± 5.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Velocity of cervical esophageal wall to close (mm/sec)</td>
<td>16.4 ± 6.0</td>
<td>15.4 ± 3.7</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

N.S.: not significant
Figure 1

(a) higher-amplitude, lower-frequency signals of myocardial tissue motion

MTI filter

signals from small, fast-moving blood cells

(b) higher-amplitude, lower-frequency signals of myocardial tissue motion

MTI filter

signals from small, fast-moving blood cells
(a) Time-displacement curve

maximum moving distance of anterior CE wall

Displacement (mm)

0 2.0 4.0 6.0

msec

(b) Time-velocity curve

velocity of CE wall opening

duration of CE wall closing

duration of CE wall opening

velocity of CE wall closing

Figure 2
Cervical esophageal wall opening time by TDI (msec)

Duration of UES opening by VF (msec)

Figure 3
Cervical esophageal wall opening time by TDI (msec)

Upper esophageal sphincter relaxation time by HRM (msec)

Figure 4
(a) Bland-Altman method (US-TDI vs. VF)  (b) Bland-Altman method (US-TDI vs. HRM)

Figure 5
Figure 6